

Angiomatous Kaposi Sarcoma: A Variant That Mimics Hemangiomas

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Abstract: We describe 14 cases of angiomatous Kaposi sarcoma (KS), a distinct histological variant of KS first mentioned by Gottlieb and Ackerman in 1988 that can easily be mistaken for a hemangioma. Intriguingly, this variant of KS has not attracted much attention and has not been studied in detail. Immunohistochemistry showed prominent staining of podoplanin (D2-40) of the neoplastic vasculature but not the preexisting vessels, suggesting lymphatic differentiation, despite the erythrocyte-filled round lumens. To test whether D2-40 staining of round vessels with erythrocytes was distinctive, we stained sinusoidal hemangiomas and cellular angiolipomas, both of which have these structures. In contrast to angiomatous KS, the vessels in both entities were podoplanin (D2-40) negative. The finding of round erythrocyte-filled vessels with podoplanin (D2-40) positivity may be distinctive for this form of KS.

Key Words: Kaposi sarcoma, hemangioma, angiolipoma, podoplanin (D2-40), lymphatic differentiation

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INTRODUCTION

Kaposi sarcoma (KS) was first described by Moritz Kaposi as “idiopathic multiple pigmented sarcoma of the skin” in the 19th century.¹ Since the outbreak of AIDS in the 1980s, KS has become a popular topic for research. Serologic testing for HIV only became available years into the epidemic, and the identification of KS was a cardinal sign of the condition. As a result, the criteria for early lesions of the condition were refined and there was delineation of a variety of vascular proliferations that simulated it. In 2010, O’Donnell et al² presented 6 cases of 5 distinctive histological variants of KS. To our eyes, the case the authors described as “glomeruloid KS” actually resembles the “angiomatous” type of KS first mentioned by Gottlieb and Ackerman³ more than 20 years ago. Intriguingly, this variant of KS did not drive much attention since its first description. We present 14 cases of angiomatous KS and discuss its differential diagnosis.

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MATERIALS AND METHODS

We retrieved 14 cases between 1991 and 2004 from the database of our service (Table 1). The specimens were fixed in 10% formalin, embedded in paraffin, and processed routinely for the investigation under light microscopy. The tissues were stained with hematoxylin and eosin (H&E).

Immunohistochemistry was performed with human herpesvirus 8 (HHV-8) latent nuclear antigen (LANA, 1:100; Vector Laboratories, Burlingame, CA, USA), anti-CD31 antibody (1:40; Dako, Laboratories, Carpinteria, CA, USA), anti- α -smooth muscle actin antibody (1:100; Dako Laboratories), anti-laminin antibody (1:250; Sigma-Aldrich Laboratories, St. Louis, MO, USA), and anti-podoplanin antibody (clone D2-40, 1:100; Dako Laboratories) in all cases; immunohistochemistry with anti-CD68 antibody (1:200; Dako Laboratories) was performed in select cases (case 4, 6, 9, 11, and 13). In addition, we retrieved 12 cases of sinusoidal hemangioma and 12 cases of cellular angiolipoma diagnosed between 2008 and 2012 from our database to perform immunostaining with podoplanin (D2-40).

RESULTS

Microscopically, sections stained with H&E showed nodular areas in the dermis, composed of plump spindle cells and thin-walled, oval-to-round dilated vessels stuffed by erythrocytes (Figs. 1, 2). The “promontory” sign, a classic feature for KS, was absent in all the cases. The lesions sometimes made a “lobular” impression because of the preserved collagen bundles between the nodular foci. They were accompanied by infiltrates of lymphocytes and plasma cells. Extravasated erythrocytes were present throughout the cases; hemosiderin and/or siderophages were also found (Fig. 3).

Positive immunohistochemical staining revealed 12 cases (86%) with staining for HHV-8 LANA. We observed HHV-8 positivity both in the stromal spindle cells and in the endothelial cells of the dilated neoplastic vessels. We failed to demonstrate HHV-8 infection in cases 4 and 11. The negative or faint expression of HHV-8 LANA is most likely caused by prolonged storage of the paraffin blocks.

Podoplanin (D2-40) (which labels podoplanin, a marker for lymphatic endothelium) stained the vasculature within the lesions in a consistent strongly positive manner. Interestingly, it only outlined the contour of those neoplastic vessels but not that of the preexisting “old” vessels. We assessed a vessel as preexistent if it had morphology similar to that of venules found in normal skin, with a narrow round lumen. CD31, a marker for vascular endothelium, was detected in the

TABLE 1. Clinical Data of Patients With Angiomatous KS

Case	Age (yrs)	Sex	Biopsy Site	Clinical Impression
1	30	Male	Thigh	KS? Dermatofibroma?
2	49	Male	Flank	R/O KS
3	69	Male	Foot	R/O KS
4	47	Male	Ankle	Insect bite?
5	39	Male	Arm	R/O melanoma
6	49	Male	Heel	KS? Contusion?
7	50	Male	Nose	R/O KS
8	40	Male	Arm	Small violaceous papule
9	Unknown	Male	Shoulder	R/O KS
10	39	Male	Chest	R/O KS
11	58	Male	Thigh	R/O KS
12	46	Male	Arm	R/O KS
13	35	Male	Calf	R/O KS
14	72	Female	Arm	R/O melanoma

preexisting blood vessels. CD31 was mostly absent in the neoplastic vessels, but it can be occasionally found weakly expressed in the cytoplasm of some stromal spindle cells and some endothelial cells of the dilated neoplastic vessels. The expression of α -smooth muscle actin followed a similar phenomenon as that of CD31. The basement membrane component laminin generally outlined all vascular structures, but its expression was significantly reduced in the dilated newly formed vessels, showing a discontinuous “fenestrated” pattern at the perimeter of the structures.

In contrast to the prominent expression of podoplanin in angiomatous KS, immunostaining with podoplanin (D2-40) was negative in all the cases of sinusoidal hemangioma and cellular angiolipoma (Fig. 4). We had chosen these entities because they contained vessels with dilated round lumens, “stuffed” with erythrocytes. Similar structures can be seen in angiomatous KS (Fig. 5).

DISCUSSION

Angiomatous KS can mimic other vascular lesions and lead to diagnostic confusion. It is sometimes encountered in the absence of other better-developed patches or plaques, and hence its recognition can be important. The vascular spaces in KS are usually irregular, branch/slit like, or bizarre shaped. It is rather exceptional for KS to show round and well-formed vessels.³ Such changes can occasionally occur in coexistence with areas in which more classic features of KS are present. However, in biopsies showing exclusively dilated vessels, as we demonstrate here, the recognition of KS as such can be challenging. This was also the concern that Gottlieb and Ackerman³ expressed when they first described the angiomatous pattern of KS. At that time (1988), the role of HHV-8 in the pathogenesis of KS was not yet elucidated. It was not until 1994 that Chang et al⁴ revealed the etiological connection between HHV-8 and KS. At present, we can use immunostaining with HHV-8 LANA to support the diagnosis of angiomatous KS, a technique not available in 1988.

As the nomenclature suggests, angiomatous KS can mimic certain benign vascular proliferations because of the

presence of thin-walled and dilated blood vessels, which are also seen, for example, in several types of hemangioma. Usually, it is not difficult to tell them apart because these hemangiomas tend to form larger vessels lined by flat endothelial cells. The distance between the dilated vessels is wider, and the lumens are occasionally occluded by thrombi.

However, it might be trickier to differentiate angiomatous KS from the so-called sinusoidal hemangioma,⁵ a lesion that was previously called cavernous hemangioma by many pathologists, which is small and does not correspond to most clinician’s understanding of that term. At scanning magnification, the 2 entities have many features in common. Both of them are composed of closely arranged and dilated vessels filled with bright red erythrocytes; both lesions can make a lobular impression. Nevertheless, at lower power, one can also readily recognize the interconnecting thin-walled vessels in a sinusoidal hemangioma, producing its unique “sinusoidal” appearance. A sinusoidal hemangioma would not have the pale areas composed of stubby spindle cells seen in angiomatous KS. The walls of the dilated vessels in an angiomatous KS are not contiguous to one another. “Back to back” vessels occur in angiomatous KS but are much more extensive in sinusoidal hemangiomas. Clinically, angiomatous KS has a male dominance in its patient population, whereas sinusoidal hemangioma occurs more often in females.

Cellular angiolipoma can be potentially confused with KS, especially in the presence of a positive clinical history of HIV/AIDS or its risk factors. Weldon-Linne et al⁶ reported 2 cases of cellular angiolipoma in homosexual men, with which the pathologists initially had diagnostic difficulties. However, pathologists are now more familiar with this entity. Angiolipoma is a tumor of adipocytes with different degrees of increased vascularity, varying from subtle vascular to dense cellular. The vascular part is usually present at the periphery. Because of the dense, perivascular spindled cell component, the resemblance of cellular angiolipoma to KS can be striking, especially if the rounded contour of the lesion cannot be discerned because of a partial biopsy. The most characteristic features of cellular angiolipoma are encapsulation, septation, and intravascular fibrin thrombi.⁷ The presence of the residual fatty cells also offers a helpful clue.

An exceedingly rare entity, spindle cell hemangioma, also possesses dilated vessels congested with erythrocytes, a feature also present in the angiomatous type of KS. However, it is usually not difficult to tell them apart clinically and histopathologically because spindle cell hemangiomas are usually solitary large lesions extending into the subcutis. Although Kaposi lesions can have this appearance, such large ones are accompanied by smaller and more superficial lesions. The endothelial cells in spindle cell hemangioma often contain intracytoplasmic lumens (so-called blister cells), a finding not seen in angiomatous KS. Miettinen and Wang⁸ demonstrated that spindle cell hemangioma expresses Prox1 transcription factor, a marker for lymphatic endothelium. The authors also indicated in the discussion section of their paper that the endothelial cells of this entity are podoplanin positive. Hence, a partial biopsy of spindle cell hemangioma could be difficult to distinguish from angiomatous KS, without staining for HHV-8 and adequate clinical information.

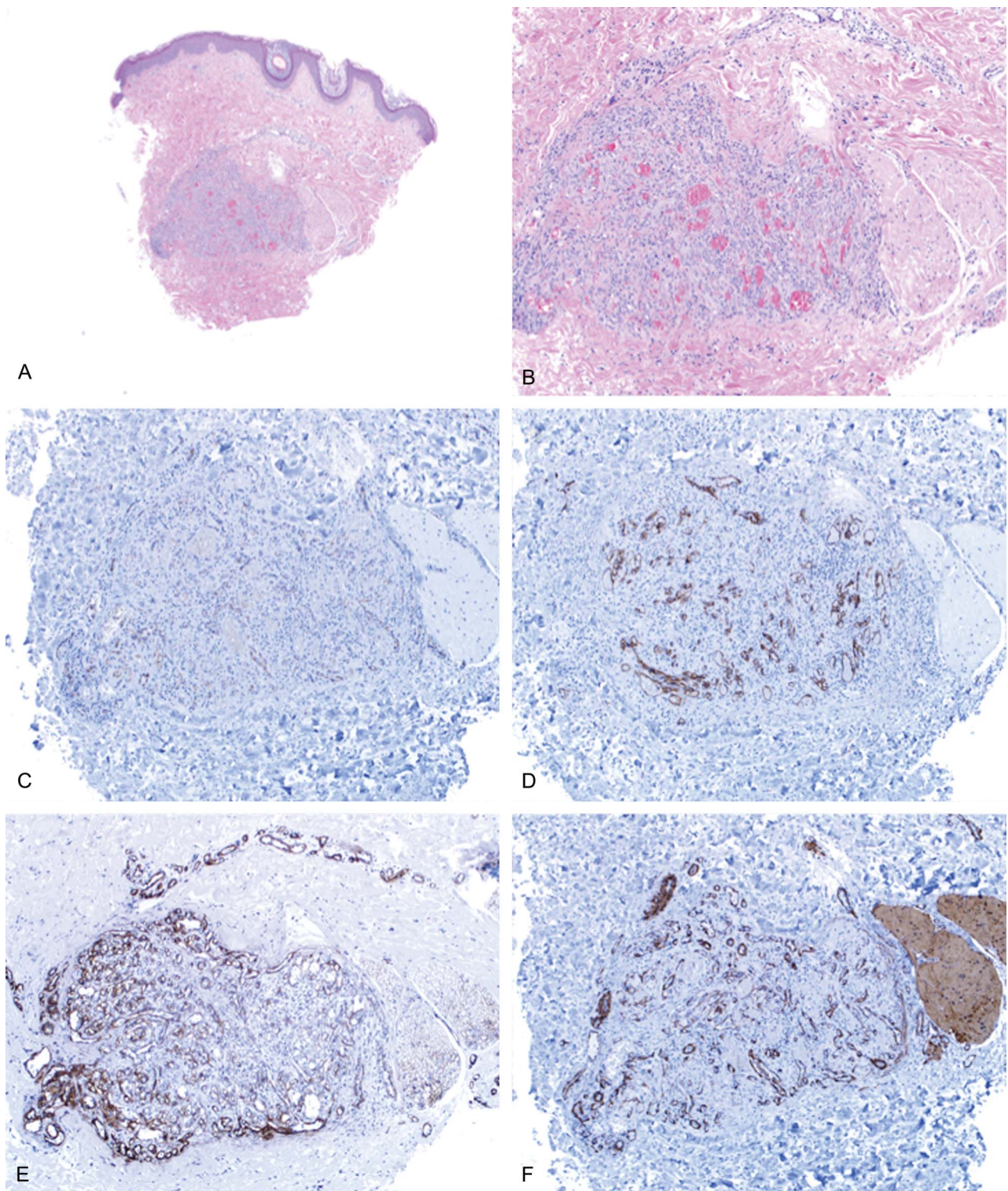


FIGURE 1. A punch biopsy from the thigh of a 30-year-old man (case 1). A, At scanning magnification, the specimen showed a nodular area of increased cellularity and vascularity in the lower dermis. B, At higher power, proliferation of plump spindle cells and dilated round vessels stuffed with erythrocytes were seen. C, CD31 expression was detected in the cytoplasm of some spindle cells and endothelial cells of preexisting vessels, but its expression was absent in the endothelium of the dilated neoplastic vessels. D, Podoplanin (D2-40), a marker for lymphatic endothelium, stained the dilated neoplastic vessels within the lesion strongly positive. E, Laminin was generally expressed in all vessels, but its expression was significantly reduced in those dilated vessels labeled by podoplanin (D2-40). F, α -SMA was strongly expressed in the preexisting vessels but only weakly expressed or absent in the dilated neoplastic vessels.

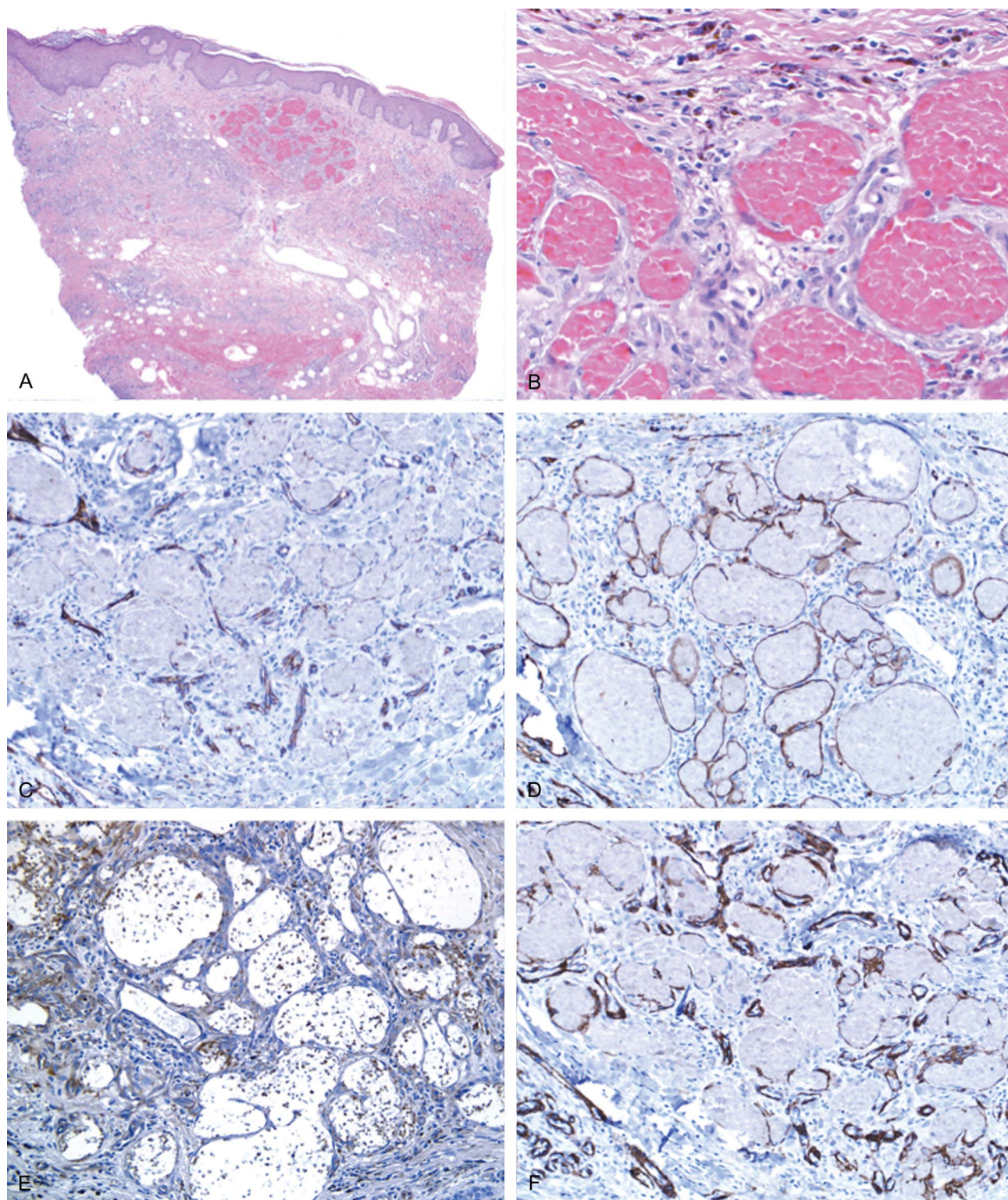
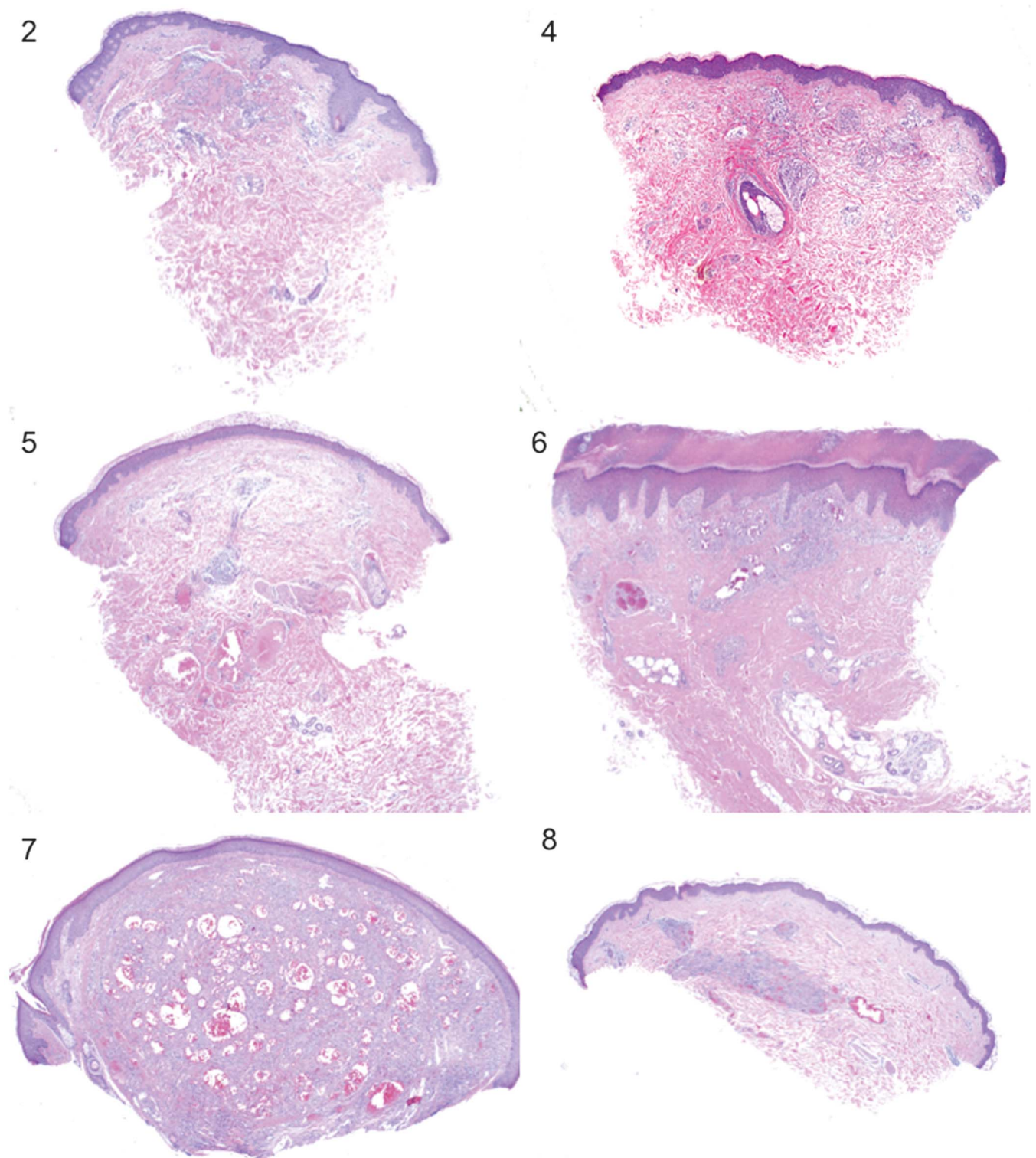
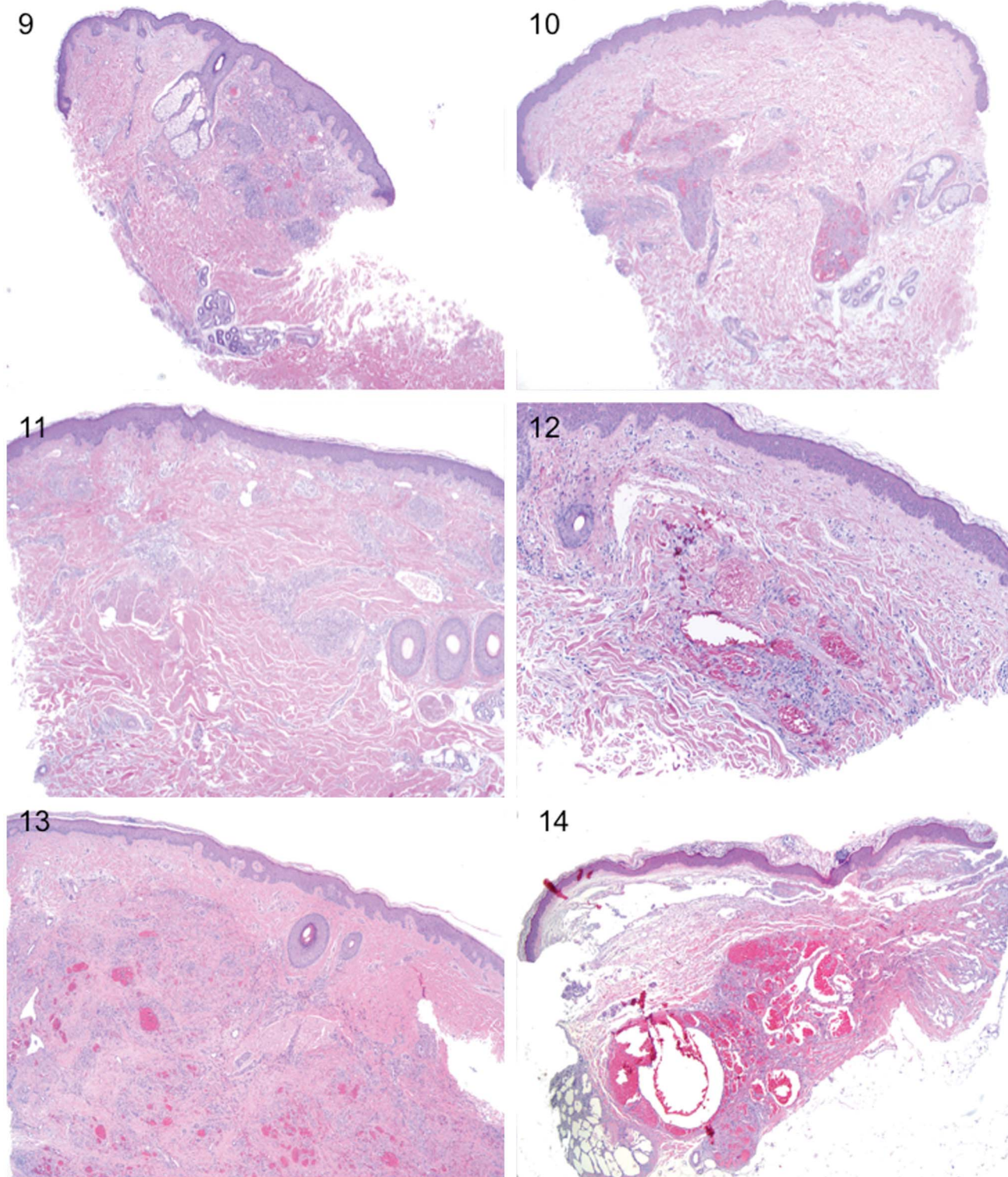


FIGURE 2. A punch biopsy from the foot of a 69-year-old man (case 3). A, At scanning magnification, a relatively well-circumscribed Kaposi lesion with oval-to-round vessels was seen in the superficial dermis, mimicking a hemangioma. B, At higher power, one can easily identify that instead of flat vascular endothelial cells, these dilated vessels were actually surrounded by plump spindle cells. C and D, Immunohistochemical results similar to those shown in Figure 1, suggesting a lymphatic differentiation of the spindle cells in KS. The tissue was stained with anti-CD31 (C), podoplanin (D2-40) (D), anti-laminin (E), and anti- α -SMA (F) antibodies.



A

FIGURE 3. Demonstration of case 2 and cases 4–8 (3A) and cases 9–14 (3B) at low-power view. Note their striking resemblance to certain benign vascular lesions, such as classic hemangioma, sinusoidal hemangioma, or pyogenic granuloma. Some lesions may give a “pseudogranulomatous” or “pseudolobular” impression. Some foci within the lesions also showed morphological similarities to the vascular areas in a cellular angiolipoma.



B

FIGURE 3. Continued

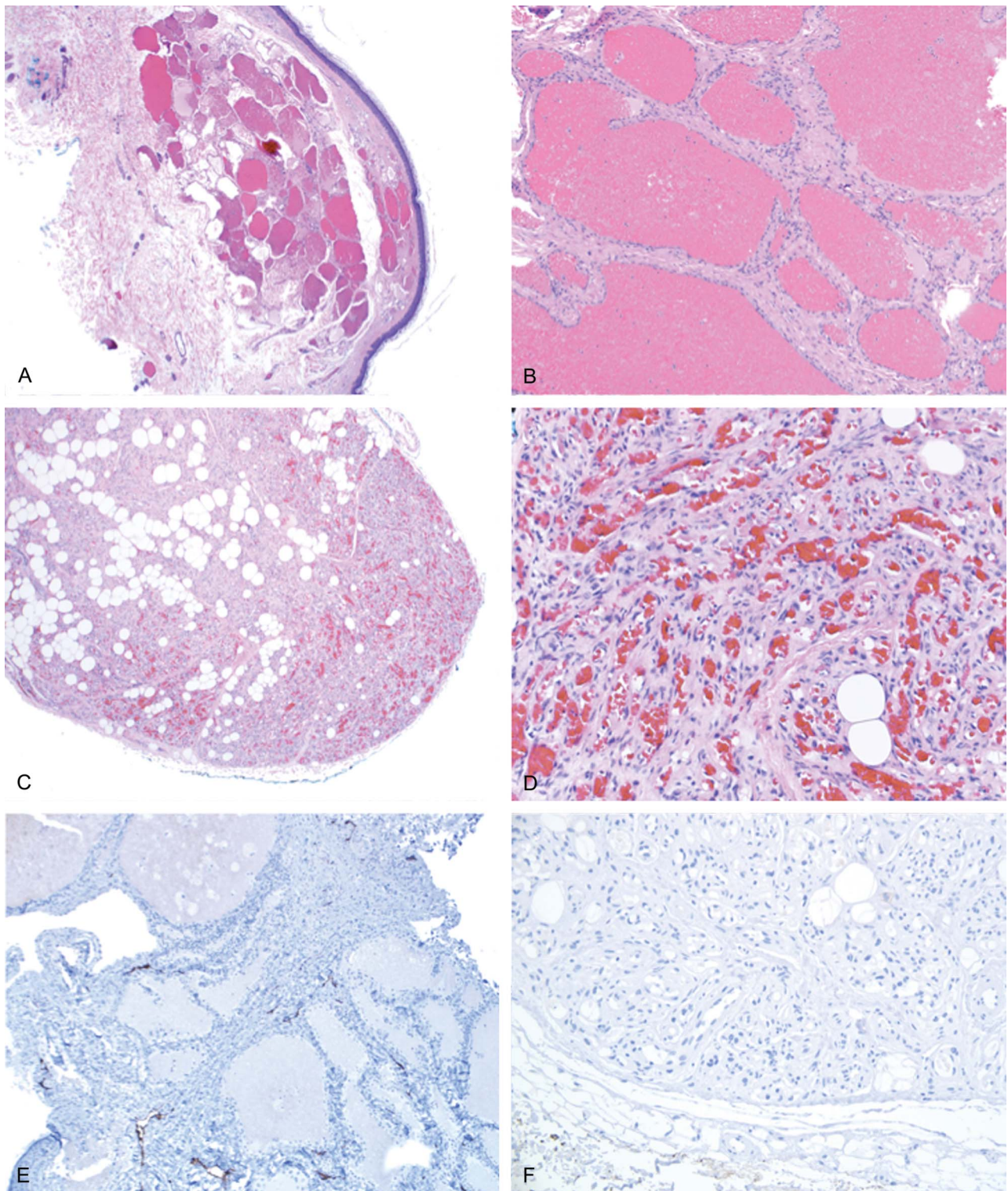


FIGURE 4. A, The shave biopsy of a sinusoidal hemangioma showed a superficial lesion with dilated vessels stuffed with erythrocytes. Note there was increased vascularity but no increased cellularity at this scanning magnification. B, The high-power view showed the characteristic "interconnecting" vessel walls. C, The low-power view of a biopsy diagnosed as cellular angioliipoma. At this power, differentiation between an angiomatous KS and a cellular angioliipoma is not difficult because of the peripheral location of the vascular part and the presence of adipocytes. D, However, there appeared to be a significant similarity at higher power. The absence of spindle cells and presence of interspersed adipocytes tell the 2 entities apart. E and F, The endothelium of dilated vessels in sinusoidal hemangiomas and cellular angioliipomas was podoplanin (D2-40) negative.

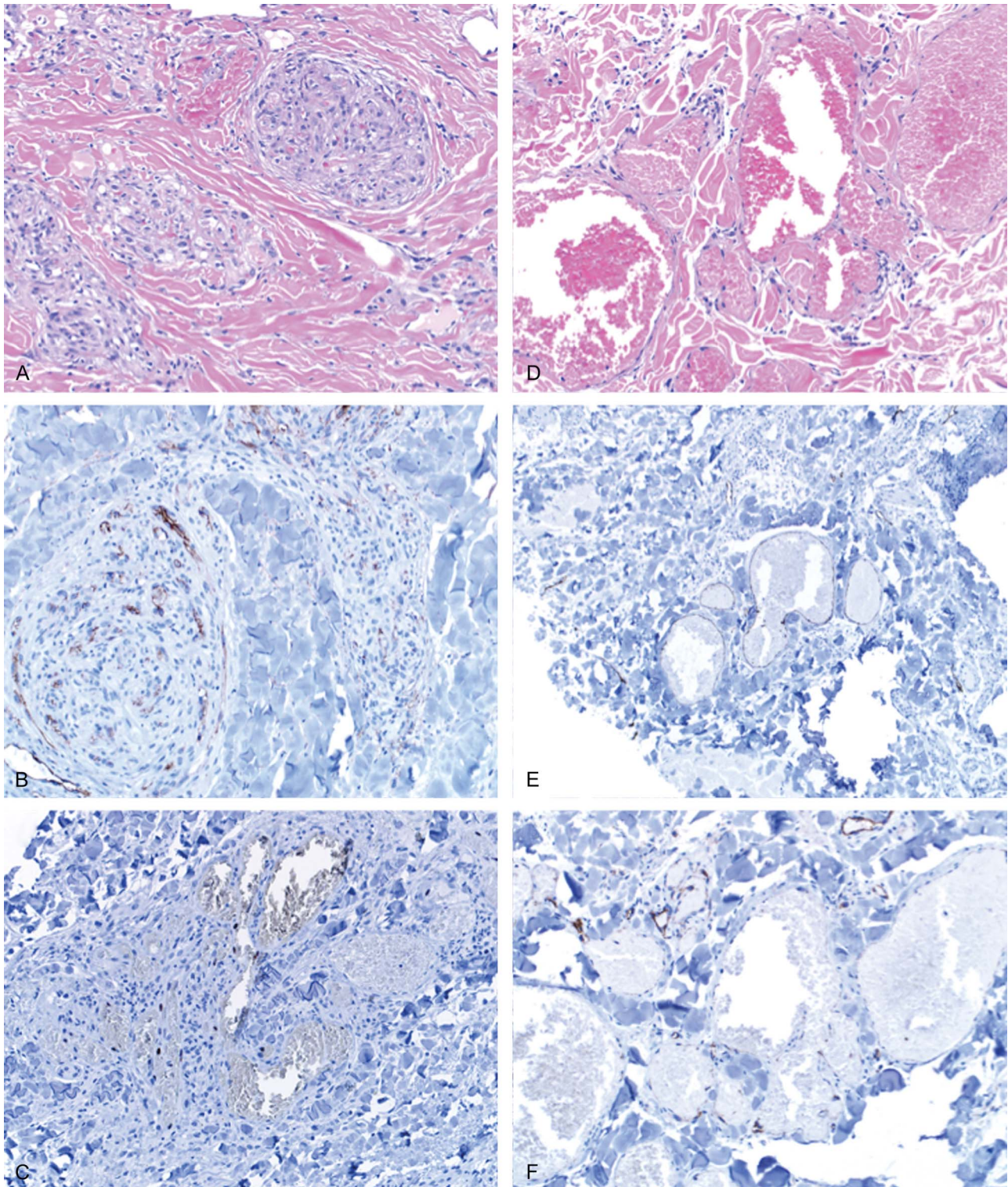


FIGURE 5. Some lesions of angiomatous KS have a glomeruloid or lobular appearance due to preserved collagen bundles between clusters of vessels (case 11). B, Podoplanin (D2-40) immunostaining showed some small neovascular structures. C, HHV-8 positivity was identified in the endothelial and stromal spindle cells. D, A closer look at a lesion of an angiomatous KS (case 5) showed its striking resemblance to a sinusoidal hemangioma (Fig. 4B). However, their vessel walls were not in apposition to one another. This patient had a history of esophageal KS diagnosed independently in the surgical pathology service. E, Podoplanin (D2-40) outlined the contour of the dilated vessels in (D). F, CD31 was expressed in the preexisting blood vessels, but the dilated vessels were CD31 negative.

TABLE 2. Summary of the Immunohistochemical Findings in Angiomatous KS

Antibody	Preexisting Vessels	Neoplastic Vessels
Anti- α -smooth muscle actin	Strong positive	Negative or weak positive
Anti-CD31	Positive	Negative or weak positive
Anti-podoplanin [clone podoplanin (D2-40)]	Negative	Strong positive
Anti-laminin	Strong positive	Moderate positive

If diagnostic difficulties were encountered because of the histological similarity between these entities, our findings showed that podoplanin (D2-40) is a powerful and consistent marker to distinguish angiomatous KS (positive staining) from sinusoidal hemangioma (negative staining) and cellular angiolipoma (negative staining). Some of our cases were negative for HHV-8, a factor we attribute to the age of the blocks, which were chosen as they came from the peak of the HIV epidemic in San Francisco. We have observed this loss of staining with conventional KS as well. The cases that we chose were limited by the marked decrease in the occurrence of KS because of the introduction of antiretroviral therapy, and our negatively stained cases occurred in patients with other evidence of HIV infection or conventional KS at other sites.

Our immunohistochemical findings provide an entrée for some interesting speculations about the pathogenesis of angiomatous KS (Table 2). The prominent and consistent staining of podoplanin (D2-40) in spindle cells suggests lymphatic differentiation. An alternative possibility is that podoplanin (which D2-40 labels) mediates cellular migration, and the vessels are not truly lymphatic but are infiltrating the adjacent dermis. This seems unlikely because many lesions of this variant are small and clinically stable. The diminished expression of laminin in the neoplastic vessel walls suggests a potential structural weakness, predisposing them to become ectatic. It is also possible that the wall structure is not altered but reflects the fenestrated basement membrane of the normal lymphatic endothelium, again suggesting a lymphatic differentiation of the spindle cells of KS.

Our observation of the erythrocyte-filled dilated vessels with strong expression of podoplanin in angiomatous KS provoked speculation as to how connections between lymphatics and blood vessels play a role in the pathogenesis and progression of KS. Interestingly, Dictor⁹ has proposed similar thoughts back in 1986. He hypothesized that the initiation of KS may be an abnormal recapitulation of the coupling of

venous and lymphatic system during embryonic growth.⁹ We considered that the erythrocyte-filled neoplastic vessels in angiomatous KS might be actually on the blood vascular side of an anastomosis between blood and lymphatic vessels but express podoplanin because of HHV-8 infection. Reprogramming of the differentiation of endothelial cells by HHV-8 can occur in cell culture systems.¹⁰ An alteration of the microcirculation, as Dictor also proposed, might be the cause of these ectatic vessels. This postulate would also account for the dilatation of these vessels because erythrocytes might be unable to squeeze through smaller spaces downstream in the spindle cell part of the microvasculature. Other conditions, such as cases of targetoid hemosiderotic hemangioma and angiosarcoma with blood-filled lumens lined by podoplanin-positive endothelial cells, may reflect different pathophysiologies.

In summary, angiomatous KS is a distinct but rare histological variant of KS, which may mimic sinusoidal hemangioma or, in partial biopsies, cellular angiolipoma in H&E-stained sections. Along with careful recognition of the histological differences, podoplanin (D2-40) is a helpful marker because it stains the endothelial cells of the round spaces that contain erythrocytes in this variant of KS, unlike the case in most hemangiomas. The prominent staining of podoplanin (D2-40) also suggests a lymphatic differentiation of the spindle cells of KS.

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